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Original Article

# Retrospective analysis of 1-month and 1-year mortality due to bleeding in patients using warfarin

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## ABSTRACT

**Aims:** Warfarin is approved for the prevention and/or treatment of venous thrombosis, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement. International normalized ratio (INR) above the therapeutic range increases the risk of bleeding, its level below the therapeutic range increases the risk of thromboembolic complications. We aimed to evaluate the effect of patients' INR levels on one-month and one-year mortality.

**Methods:** The hospital's electronic information management system retrospectively screened between 01.01.2015, and 31.12.2016. Patients who applied to the emergency department (ED) with a history of warfarin use, were included in the study. The receiver operating characteristics (ROC) analysis and the area under the curve (AUC) for the mortality estimation calculations were used for statistical analysis.

**Results:** Total of 1299 patients with elevated INR due to warfarin use were included in the study. The major ED admission causes were bleeding (n=338, 26.02%) and INR control with no other complaint (n=56, 4.31%). Mortality was observed within one month in 118 (9.1%) patients and within one year in 292 (22.5%) patients. The ROC analysis for 1-month and 1-year mortality estimation, AUC values for age, INR, urea, and creatinine were 0.640, 0.549, 0.702, 0.629 and 0.629, 0.532, 0.671, 0.608, respectively.

**Conclusion:** The patients admitted to ED due to high INR values are usually corrected their INR values and then discharged. These patients' one-year mortality is high so to identify and eliminate the underlying cause of the INR elevation is important.

**Keywords:** Warfarin, emergency department, mortality, international normalized ratio

## INTRODUCTION

Warfarin is approved for the prevention and/or treatment of venous thrombosis, pulmonary embolism, and thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement and to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events after myocardial infarction.[1]

Warfarin and other vitamin K antagonists (VKA) (acenocoumarol, phenprocoumon, fluindione) are used in various clinical settings. Warfarin is still widely used, despite increasing interest and investigations focused on the effectiveness of direct oral anticoagulants (DOACs).[2] Their use is challenging because their therapeutic range is narrow, and dosing is affected by many factors, including genetic variation, drug interactions, and diet.[3] On the other hand, while international normalized ratio (INR) above the therapeutic range increases the risk of bleeding, its level below the therapeutic range increases the risk of thromboembolic complications.[4] So, there is a need for frequent monitoring and the associated risk of bleeding and other side effects.[5]

This study is aimed to evaluate the effect of patients' INR levels on one-month and one-year mortality.

## METHODS

This retrospective observational study was conducted in a tertiary education and research hospital with 450.000 patient admissions annually. This study was conducted in accordance with the 1989 Declaration of Helsinki and was approved by the local ethics committee. This study was approved by the Clinical Researches Ethics Committee of University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital (Date: 17.10.2017, Decision No: 870). Patients who applied to the emergency department (ED) between January

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1, 2015, and December 31, 2016, with a history of warfarin use, were included in the study. We retrospectively screened the hospital's electronic information management system and patient charts. Gastrointestinal bleeding, hematuria, mucosal bleeding, abdominal pain, and ecchymosis were considered side effects. Exclusion criteria were missing data and younger than 18 years of age.

We recorded demographic data, warfarin indications, primary complaints at ED admission, Complete blood count (CBC), INR, prothrombin time (PT), activated partial thromboplastin time (aPTT), urea, creatinine, AST, ALT results, and treatments given in the ED. One-month and one-year mortality were retained from the nationwide demographics system. The primary outcome was the length of stay time (LOS). Secondary outcomes were one-month and one-year mortality rates.

### Statistical Analysis

We used the Kolmogorov-Smirnov test for the normal distribution of data. Results were reported as mean±standard deviation (SD) for continuous variables with normal distribution; median and interquartile range (IQR) for non-normally distributed variables; and frequency and percentage for categorical variables. The contribution of the variables to mortality prediction was evaluated with multivariate regression analysis, and the odd's ratio was calculated. We performed a Kaplan-Meier analysis for the mortality rate analysis. A p-value of <0.05 was considered statistically significant. We used SPSS 20.0 statistical package for the analyses.

## RESULTS

We included a total of 1299 patients with elevated INR due to warfarin use in the study. 45.1% (n=586) of the patients were male, the mean age was 68.4±14.9 (min-max: 18-104) years, and the mean INR value was 4.2±2.1 (min-max: 2.5-14.2).

Indications for warfarin were atrial fibrillation (AF) 39.2% (n=509), deep vein thrombosis (DVT) 1.8% (n=23), cardiac valve replacement 35.4% (n=460), stroke 22.2% (n=288), and others % 1.5 (n=19).

The major ED admission causes were bleeding (n=338, 26.02%) and INR control with no other complaint (n=56, 4.31%). The distribution of bleeding symptoms by systems is given in Table 1. In the comparison of the patients presenting with bleeding symptoms and without bleeding symptoms, the INR values were 4.9±2.6 (2.5–14.2) and 3.9±1.8 (2.5–14.0), respectively, and there was a statistically significant difference between the groups (p<0.001).

**Table 1.** The distribution of bleeding symptoms by systems

| | n | % |
|---|---|---|
| Cardiovascular | 2 | 0.6 |
| Thorax | 7 | 2.1 |
| Musculoskeletal | 162 | 47.9 |
| Gastrointestinal | 68 | 20.1 |
| Genitourinary | 69 | 20.4 |
| Ear nose throat | 30 | 8.9 |
| Total | 338 | 100.0 |

The treatments given in the ED were erythrocyte suspension (n=110, 8.5%), fresh frozen plasma (n=183, 14.1%), and vitamin K (n=229, 17.6%). 986 (75.9%) patients were followed without treatment.

Mortality was observed within one month in 118 (9.1%) patients and within one year in 292 (22.5%) patients. Age, APTT, white blood cell (WBC), hemoglobin (HGB), platelet (PLT), urea, creatinine, AST, vitamin K treatment, and follow-up without treatment showed statistically significant differences between patients who died and survived within one month (p<0.05). Besides, compared to the one-year mortality, age, APTT, WBC, HGB, PLT, urea, creatinine, and AST values showed a statistically significant difference between mortality and non-mortality groups (p<0.05). INR value did not show a statistically significant difference between the groups for one-month and one-year mortality (Table 2).

In multivariate logistic regression analysis for 1-month mortality, age (p=0.000, odds ratio: 1.049), WBC (p=0.042, odds ratio: 1.028), urea (p=0.002, odds ratio: 1.007) and AST (p=0.016, odds ratio: 1.002) was identified as an independent risk factor. Besides, age (p=0.000, odds ratio: 1.030), aPTT (p=0.000, odds ratio: 1.013), WBC (p=0.046, odds ratio: 1.028), urea (p=0.000, odds ratio: 1.011) and creatinine (p=0.022, odds ratio: 0.807) were determined as independent risk factors in the multivariate logistic regression analysis for 1-year mortality.

Kaplan-Meier analysis showed a mortality rate of 9.1% for 1-month and 22.5% for 1-year and estimate survive time was 292 days at INR ≥3.5 group and 306 days at INR <3.5 group (Figure).

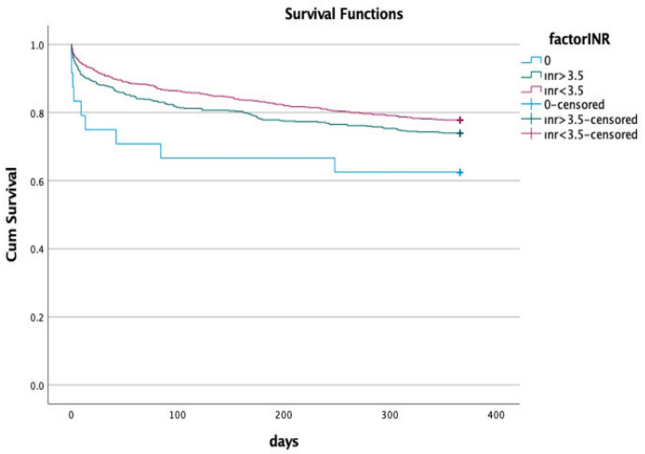


**Figure.** Mortality of the patients according to Kaplan–Meier analysis
INR: International normalized ratio

## DISCUSSION

We primarily concluded that patients with high INR levels admitted to ED have high one-year mortality rates, and age, aPTT, WBC, HGB, PLT, urea, creatinine, and AST values are independent factors.

To the best of our knowledge, no study that includes all warfarin-related side effects has been reported in the current literature.[6] One-month and one-year mortality were studied only for bleeding due to warfarin-induced high INR in the

**Table 2.** Comparison of demographic data and laboratory results

| | | One month mortality | | | | | | One year mortality | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | Mean | SD | Lower | Upper | p | n | Mean | SD | Lower | Upper | p |
| **Age** | Survive | 1181 | 67.64 | 15.17 | 18 | 104 | <0.001 | 1007 | 66.73 | 15.35 | 19 | 101 | <0.001 |
| | Mortal | 118 | 75.81 | 10.40 | 39 | 94 | | 292 | 74.07 | 12.00 | 18 | 104 | |
| **INR** | Survive | 1181 | 4.13 | 2.10 | 2.50 | 14.20 | 0.304 | 1007 | 4.14 | 2.12 | 2.50 | 14.2 | 0.688 |
| | Mortal | 118 | 4.34 | 2.08 | 2.50 | 12.50 | | 292 | 4.19 | 1.99 | 2.50 | 14 | |
| **PT** | Survive | 1181 | 53.10 | 29.95 | 6.88 | 349 | 0.383 | 1007 | 53.18 | 30.71 | 6.88 | 346 | 0.744 |
| | Mortal | 118 | 55.61 | 28.07 | 11.7 | 159 | | 292 | 53.83 | 26.40 | 11.70 | 159 | |
| **aPTT** | Survive | 1179 | 65.78 | 27.71 | 5.29 | 251.10 | <0.001 | 1005 | 65.62 | 27.34 | 5.29 | 251.10 | 0.005 |
| | Mortal | 118 | 77.79 | 41.70 | 27 | 240 | | 292 | 71.17 | 35.47 | 27 | 240 | |
| **WBC** | Survive | 1105 | 9.51 | 3.99 | 1.48 | 46.40 | <0.001 | 937 | 9.35 | 3.73 | 1.48 | 46.40 | <0.001 |
| | Mortal | 117 | 11.84 | 7.13 | 0.53 | 51.57 | | 285 | 10.99 | 6.04 | 0.53 | 51.57 | |
| **HGB** | Survive | 1106 | 11.96 | 2.39 | 2.80 | 18.30 | <0.001 | 937 | 12.01 | 2.35 | 2.80 | 18.30 | <0.001 |
| | Mortal | 117 | 10.98 | 2.61 | 3 | 17.40 | | 286 | 11.39 | 2.63 | 3 | 17.40 | |
| **PLT** | Survive | 1105 | 252.03 | 90.68 | 25 | 979 | 0.021 | 936 | 252.70 | 88.96 | 25 | 979 | 0.068 |
| | Mortal | 117 | 231.55 | 96 | 47 | 740 | | 286 | 241.44 | 98.50 | 39 | 767 | |
| **Urea** | Survive | 1046 | 59.38 | 45.43 | 0.61 | 404.40 | <0.001 | 882 | 55.92 | 41.94 | 0.61 | 404.40 | <0.001 |
| | Mortal | 117 | 97.06 | 71.46 | 18.90 | 396 | | 281 | 85.95 | 64.27 | 15 | 396 | |
| **CREA** | Survive | 1046 | 1.29 | 1.33 | 0.25 | 27.10 | <0.001 | 882 | 1.27 | 1.37 | 0.25 | 27.10 | <0.001 |
| | Mortal | 117 | 1.85 | 1.54 | 0.18 | 7.81 | | 281 | 1.58 | 1.29 | 0.17 | 7.81 | |
| **ALT** | Survive | 1045 | 26.38 | 59.33 | 0 | 810.10 | <0.001 | 882 | 25.52 | 58.59 | 0 | 810.10 | 0.005 |
| | Mortal | 117 | 59.23 | 217.47 | 1.80 | 2270.60 | | 281 | 42.76 | 148.69 | 1.60 | 2270.60 | |
| **AST** | Survive | 1045 | 33.30 | 85.13 | 1.13 | 1622 | <0.001 | 882 | 31.74 | 85.86 | 2.30 | 1622 | 0.001 |
| | Mortal | 117 | 111.54 | 488.50 | 4.30 | 5120.30 | | 281 | 70.77 | 322.27 | 1.13 | 5120.30 | |

SD: Standard deviation, INR: International normalized ratio, PT: Prothrombin time, aPTT: Activated partial thromboplastin time, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, CREA: Creatinine

ED. In our study, one-month and one-year mortality were relatively high. In high INR value patients, Conti et al.[6] also found similar mortality rates for 1-month and 1-year at 6% and 17%, respectively.

In various studies conducted in this area, the high-risk age has been reported as 65.14±14.8, 64.2±13.3, and 68.8 (29-85).[7-9] In our study, the mean age of the patients was 68.4±14.9 (18-104), which was considered compatible with the literature. Many studies have determined that the risk of high INR due to the use of warfarin increases in elderly patients. This may be due to inadequate drug compliance, increased risk of other drug interactions due to multiple drug use, and decreased warfarin clearance by age.[10,11]

In addition, in our study, in terms of 1-month and 1-year mortality, age, aPTT, WBC, HGB, PLT, urea, creatinine, and AST values were found to differ between mortality and non-mortality groups. The reasons for the difference in these parameters are considered as the low physiological reserve in advanced ages; aPTT, HGB, and PLT indicate the severity of blood loss due to coagulopathy and bleeding complications; WBC elevation secondary to early stressor response; co-morbidities and drug use triggering AST elevation; and warfarin is preferred over DOACs in patients with chronic renal failure. While vitamin K treatment made a difference between the mortality and non-mortality groups for 1-month mortality, that was not valid for 1-year mortality.

Since warfarin pharmacokinetics are complicated, its therapeutic index is narrow and affected by many factors. It has been reported that INR values of ≤2 increase the thromboembolism risk, and INR values of ≥5 increase the risk of significant bleeding.[12] Close monitoring is recommended to keep the INR level in the range of 2-3. In our study, in which we included patients who developed bleeding complications due to warfarin treatment, the INR values were 4.2±2.1 (2.5–14.2), in line with the literature. No significant correlation was reported between INR level and major bleeding.[13-15] In our study, the INR value was higher in patients with bleeding symptoms than in those who do not have a bleeding complication. In addition, we found that high INR did not affect one-month and one-year mortality rates. Still, bleeding complications were not divided into major and minor in our study.

Drug interactions or superimposed conditions (e.g., liver disease, malabsorption) that may interfere with warfarin ingestion, absorption, or metabolism are the most common causes of a supratherapeutic INR. In our study, the most common indication among the patients with a high INR was AF. Due to all these reasons, while warfarin is widely used, especially in patients with chronic kidney disease or heart valve replacement, DOACs are preferred anticoagulants.[3,5]

## CONCLUSION

The patients admitted to ED due to high INR values are usually corrected their INR values and then discharged. Especially keeping in mind that their one-year mortality is high, we recommend to identify and eliminate the underlying cause of the INR elevation and to follow up with these patients more closely.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

This study was approved by the Clinical Researches Ethics Committee of University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital (Date: 17.10.2017, Decision No: 870).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

### Financial Disclosure

The authors declared that this study has received no financial support.

### Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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